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From the INTERNATIONAL BUREAU

RECD PCT/PTO 04 MAR 2005

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

ELRIFI, Ivor, R.
Mintz, Levin, Cohn, Ferris, Glovsky, and Popeo, P. C.
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 18 March 2004 (18.03.2004)	
Applicant's or agent's file reference 17811-017CIP	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2003/027888	05 September 2003 (05.09.2003)	06 September 2002 (06.09.2002)

Applicant

ISOTIS S.A. et al

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   AU, AZ, BY, CH, CN, CO, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-*bis*)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 18 March 2004 (18.03.2004) under No. WO 2004/022077

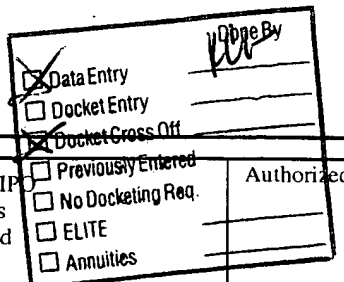
4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

   The applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

   In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   For filing a **demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

   It is the applicant's **sole responsibility** to monitor all these time limits.



The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Gijsbertus Beijer - Carlos Roy

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING THE FILING OF AMENDMENTS OF THE CLAIMS

(PCT Administrative Instructions, Section 417)

To:

ELRIFI, Ivor, R.
Mintz, Levin, Cohn, Ferris, Glovsky, and Popeo, P. C.
One Financial Center
Boston, MA 02111
United States of America

Date of mailing (day/month/year) 17 February 2004 (17.02.2004)	
Applicant's or agent's file reference 17811-017CIP	**IMPORTANT NOTIFICATION**
International application No. PCT/US2003/027888	**International filing date** (day/month/year) 05 September 2003 (05.09.2003)
Applicant ISOTIS S.A. et al	

1. The applicant is hereby notified that amendments to the claims under Article 19 were received by the International Bureau on:

   02 February 2004 (02.02.2004)

2. This date is within the time limit under Rule 46.1.

   Consequently, the international publication of the international application will contain the amended claims according to Rule 48.2(f), (h) and (i).

3. The applicant is reminded that the international application (description, claims and drawings) may be amended during the international preliminary examination under Chapter II, according to Article 34, and in any case, before each of the designated Offices, according to Article 28 and Rule 52, or before each of the elected Offices, according to Article 41 and Rule 78.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. (41-22) 338.71.40

Authorised officer
Jorge KREPELKA
Telephone No. (41-22) 338 9198

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
IVOR R. ELRIFI
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	
Applicant's or agent's file reference 17811-017CIP	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/27888	05 September 2003 (05.09.2003)	06 September 2002 (06.09.2002)

Applicant

ISOTIS SA

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Christopher J Nichols, Ph.D.

Telephone No. 703-308-0196

Form PCT/IPEA/416 (July 1992)

RECEIVED
SEP 02 2004
MINTZ LEVIN, BOSTON
PATENT DOCKET DEPT

Done By
- ☐ Data Entry
- ☒ Docket Entry 11/30
- ☒ Docket Cross Off
- ☐ Previously Entered
- ☐ No Docketing Req.
- ☐ ELITE
- ☐ Annuities

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
IVOR R. ELRIFI
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	31 AUG 2004

Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
17811-017CIP	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/27888	05 September 2003 (05.09.2003)	06 September 2002 (06.09.2002)

Applicant

ISOTIS SA

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Name and mailing address of the IPEA/US
Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Christopher J Nichols, Ph.D.
Telephone No. 703-308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 17811-017CIP	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/27888	International filing date *(day/month/year)* 05 September 2003 (05.09.2003)	Priority date *(day/month/year)* 06 September 2002 (06.09.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 35/00, 48/00; C07K 5/00, 14/00; C12N 15/85, 15/86 and US Cl.: 424/93.1; 435/325; 514/44; 530/300, 350, 399		
Applicant ISOTIS SA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06 April 2004 (06.04.2004)	12 August 2004 (12.08.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Christopher J. Nichols, Ph.D. Telephone No. 703-308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
PCT/US03/27888

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-52 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages NONE, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages 53-58, filed with the letter of 08 July 2004 (08.07.2004).

☒ the drawings:
pages 1-13, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☒ the claims, Nos. 43-91

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-42	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-42	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-42	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-42 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the invention.

Claims 1-42 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

1. A cell preparation for tissue regeneration comprising

a) a first component comprising an extracellular matrix or matrix material containing fibrinogen, wherein the extracellular matrix material is selected from the group consisting of collagens, alginate, alginate beads, agarose, fibrin, fibrin glue, blood plasma, fibrin beads, laminins, proteoglycans, fibronectins, chitosan, and heparin; and

b) a second component comprising from about 1 x 10^3 cells/µl to about 50 x 10^3 cells/µl and thrombin to the wound site, wherein the cells comprise one or more keratinocytes and fibroblasts that secrete one or more biologically active molecules selected from the group consisting of GM-CSF, VEGF, KGF, bFGF, TGFβ, angiopoietin, EGF, IL-Iβ, IL-6, IL-8, TGFα, and TNFα, and wherein the one or more keratinocytes and fibroblasts are allogeneic and mitotically active or inactivated.

2. The cell preparation of claim 1, wherein the one or more keratinocytes and fibroblasts are differentiated fibroblasts and keratinocytes.

3. The cell preparation of claim 1, wherein the cell preparation is in the form of a paste.

4. The cell preparation of claim 1, wherein the cell preparation is in the form of a spray.

5. The cell preparation of claim 1, wherein the one or more keratinocytes and fibroblasts are mitotically inactivated by administration of mitomycin C or other chemically-based mitotic inhibitors, irradiation with γ-Rays, irradiation with X-Rays, or irradiation with UV light.

6. The cell preparation of claim 1, wherein the one or more keratinocytes and fibroblasts are immortalized using at least one gene/polypeptide selected from the group consisting of the 12S and 13S products of the adenovirus *E1A* genes,

hTERT, SV40 small T antigen, SV40 large T antigen, papilloma viruses E6 and E7, the Epstein-Barr Virus (EBV), Epstein-Barr nuclear antigen-2 (EBNA2), human T-cell leukemia virus-1 (HTLV-1), HTLV-1 tax, *Herpesvirus saimiri* (HVS), mutant p53, *myc*, *c-jun*, *c-ras*, *c-Ha-ras*, *h*-ras, v-*src*, *c-fgr*, *myb*, *c-myc*, *n*-myc, and *Mdm2*.

7. The cell preparation of claim 1, wherein the one or more keratinocytes and fibroblasts naturally secret one or more biologically active molecules.

8. The cell preparation of claim 1, wherein the one or more keratinocytes and fibroblasts are genetically engineered to secrete an exogenous level of one or more biologically active molecules.

9. The cell preparation of claim 1, wherein the secretion of the one or more biologically active molecules is controlled by gene switching.

10. The cell preparation of claim 1, wherein the one or more biologically active molecules is constitutively secreted.

11. The cell preparation of claim 1, wherein the first component comprises fibrinogen.

12. The cell preparation of claim 1, wherein the second component optionally further comprises a cryoprotectant.

13. The cell preparation of claim 12, wherein the cryoprotectant is selected from the group consisting of a 10% glycerol solution, a 15% glycerol solution, and a 15% glycerol and 5% human serum albumin solution

14. The cell preparation of claim 13, wherein the cryoprotectant is glycerol.

15. A kit comprising, in one or more containers, the cell preparation of claim 1.

16. The kit of claim 15, wherein the first component and the second component are cryopreserved prior to shipping and subsequently thawed prior to use.

17. The kit of claim 16, wherein the first and second components are each contained in a separate vial having a removable screw cap, wherein the vial is sterile and is made of a material resistant to low temperatures and wherein the removable lid can be replaced with a spray pump following thawing of the first and second components prior to use.

18. The kit of claim 17, wherein the spray pump delivers a volume of approximately 130 µl per spray.

19. The kit of claim 17, wherein the material resistant to low temperatures is selected from the group consisting of glass, polypropylene, polyethylene, and ethylene vinyl acetate (EVA).

20. The kit of claim 17, wherein the vials are sealed within a pouch or container prior to cryopreservation, wherein the pouch or container is fabricated of a material capable of withstanding temperatures ranging from -80°C to -196°C and wherein the pouch or container protects the first and second components from contamination during cryopreservation and subsequent thawing.

21. The kit of claim 20, wherein the pouch or container is waterproof and has a high barrier performance.

22. A method of using the kit of claim 15, the method comprising

a) administering the first component to a wound site on a patient in need of treatment; and

b) combining the second component with the first component wherein the combination of the first component and the second component forms a cell preparation suitable for tissue regeneration.

23. The method of claim 22, wherein the cell preparation is in the form of a paste.

24. The method of claim 22, wherein the cell preparation is in the form of a spray.

25. The method of claim 22, wherein the second component optionally further comprises a cryoprotectant.

26. The method of claim 25, wherein the cryoprotectant is selected from the group consisting of a 10% glycerol solution, a 15% glycerol solution, and a 15% glycerol and 5% human serum albumin solution

27. The method of claim 22, wherein the first and second components are topically administered to the wound site on the patient.

28. The method of claim 22, wherein the first and second components are sprayed onto the wound site on the patient.

29. The method of claim 28, wherein the first and second components are combined on the wound site.

30. The method of claim 28, wherein the first and second components are combined before reaching the wound site.

31. A method of administering cell preparation of claim 1 to a wound site on a patient in need of treatment, the method comprising

a) providing the first component;

b) providing the second component;

c) combining the first and second components to form the cell preparation; and

d) administering the cell preparation to the wound site.

32. The method of claim 31, wherein the first and second components are topically applied to the wound site

33. The method of claim 31, wherein the first component is applied to the wound site before the second component is applied to the wound site.

34. The method of claim 31, wherein the second component is applied to the wound site before the first component is applied to the wound site.

35. The method of claim 31, wherein the cell preparation is in the form of a paste.

36. The method of claim 31, wherein the cell preparation is in the form of a spray.

37. The method of claim 31, wherein the second component optionally further comprises a cryoprotectant.

38. The method of claim 37, wherein the cryoprotectant is selected from the group consisting of a 10% glycerol solution, a 15% glycerol solution, and a 15% glycerol and 5% human serum albumin solution

39. The method of claim 31, wherein the first and second components are sprayed on the wound site.

40. The method of claim 39, wherein the first component is sprayed on the wound site before the second component is sprayed on the wound site.

41. The method of claim 39, wherein the sprayed first and second components are combined on the wound site.

42. The method of claim 39, wherein the sprayed first and second components are combined before reaching the wound site.